(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 398 032 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
17.03.2004 Bulletin 2004/12

(21) Application number: **03020417.6**

(22) Date of filing: **10.09.2003**

(51) Int Cl.[7]: **A61K 31/517**, C07D 239/95, C07D 401/12, C07D 405/12, A61P 3/06

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

(30) Priority: **10.09.2002 EP 02020255**

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(54) 4-Oxo-quinazolines as LXR nuclear receptor binding compounds

(57) The present invention relates to 4-oxo-quinazolines which bind to the Liver X receptors (LXR receptors, LXRalpha/NR1 H3 and LXRbeta/NR1H2) and act as selective agonists of the LXR receptors. The invention further relates to the treatment of diseases and/or conditions through binding of said nuclear receptors and selective agonistic effects by said compounds and the production of medicaments using said compounds. In particular the compounds are useful in the treatment of hypercholesterimia, obesity or other diseases associated with elevated lipoprotein (LDL) levels.

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Description

[0001] Liver X Receptor (LXR) is a prototypical type 2 nuclear receptor which activates genes upon binding to promoter region of target genes in a prototypical heterodimeric fashion with Retinoid X Receptor (hereinafter RXR, Forman et al., Cell, 81, 687-93, 1995). The term LXR includes all subtypes of this receptor. Specifically LXR includes LXRa (also known as LXRalpha, RLD-1 and NR1H3) and LXRb (also known as LXRbeta, NER, NER1, UR, OR-1, R1P15 and NH1H2) and ligands of LXR should be understood to include ligands of LXRa or LXRb. The relevant physiological ligands of LXR seem to be oxidized derivatives of cholesterol, including 22-hydroxycholesterol and 24,25(S)-epoxycholesterol (Lehmann, et al., Biol. Chem. 272(6), 3137-40, 1997). The oxysterol ligands bound to LXR were found to regulate the expression of several genes that participate in cholesterol metabolism (Janowski, et al., Nature, 383, 728-31, 1996).

[0002] LXR is proposed to be a hepatic oxysterol sensor. Upon activation (e.g. binding of oxysterols) it influences the conversion of dietary cholesterol into bile acids by upregulating the transcription of key genes which are involved in bile acid synthesis such as CYP7A1. Hence, activation of LXR in the liver could result in an increased synthesis of bile acids from cholesterol which could lead to decreased levels of hepatic cholesterol. This proposed LXR function in hepatic cholesterol metabolism was experimentally confirmed using knockout mice. Mice lacking the receptor LXRa lost their ability to respond normally to an increase in dietary cholesterol and did not induce transcription of the gene encoding CYP7A1. This resulted in accumulation of large quantities of cholesterol in the livers and impaired hepatic function (Peet, et al., Cell, 93, 693-704, 1998).

[0003] Besides its important function in liver, LXR plays an important role in the regulation of cholesterol homeostasis in macrophages and intestinal mucosa cells where it upregulates cholesterol transporters from the ABC (=ATP binding cassette) family of membrane proteins (Repa, et al., J Biol Chem. 2002 May 24;277(21):18793-800).

[0004] These transporters are believed to be crucially involved in the uptake of cholesterol from the diet since mutations in their genes leads to diseases such as sitosterolemia (Berge, et al., Science (2000);290(5497):1771-5.).

[0005] Other members of the ABC transporter family seem to be responsible for the efflux of cholesterol from loaded macrophages, a process which is thought to prevent the generation of atherosclerotic lesions. Stimulation of LXR by synthetic ligands might result in an increased cholesterol efflux from macrophages and a decreased building up of cholesterol loaded atherosclerotic plaques (Venkateswaran, et al., PNAS (2000) 24;97(22):12097-102; Sparrow, et al., J Biol Chem (2002) 277(12):10021-7; Joseph, et al., PNAS (2002);99(11):7604-9). Direct evidence that synthetic LXR ligands inhibit the development of atherosclerosis has been provided in two animal models of atherosclerosis: A significant reduction in the formation of atherosclerotic plaques were shown in two studies in animal models using full LXR agonists Joseph et al. PNAS (2002) 99:7604-9 and Terasaka et al. (2003) Terasaka et al. FEBS Lett. (2003) 536: 6-11. In addition, two recent reports have highlighted the potential use of LXR agonists in diabetes (Cao et al., (2003) J Biol Chem. 278:1131-6 and inflammatory disorders (Joseph et al., (2003) Nat Med. 9:213-9.

[0006] However, in animal studies it was observed that activation of LXR in the liver by full agonists like T0901317 does not only increase bile acid synthesis but also stimulates the de novo synthesis of fatty acids and triglycerids through the upregulation of key enzymes such as Fatty Acid Synthase (FAS) or Stearyl-CoA Desaturase (SCD-1) (Schultz, et al., Genes Dev (2000) 14(22):2831-8). Elevation of serum triglyceride levels is an indendent risk factor for atherosclerosis (for review see Miller (1999) Hosp Pract (Off Ed) 34: 67-73.).

[0007] Thus, LXR activity needs to be selectively modulated for therapeutic benefit. In particular, compounds need to be found that stimulate reverse cholesterol transport, but do not significantly increase trigclyceride levels. This might be particular relevant for the usage of such compounds in diabetic patients since a even more severe lopogenic effect was reported for the full agonist T0901317 in db/db mice which serve as an animal model for diabetes (Chisholm et al. (2003) J.Lipid Res (epub August 16)).

[0008] Therefore, an ideal synthetic LXR binding compound should have properties that retain the agonistic activity on hepatic bile acid formation and ABC-transporter-mediated decrease in cholesterol uptake from the diet and increased cholesterol efflux from macrophages. In parallel such a compound should lack the hyperlipidemic potential which is exerted through increased fatty acid and triclyceride synthesis.

[0009] To date only few compounds have been described which bind the LXR receptor and thus show utility for treating diseases or conditions which are due to or influenced by said nuclear receptor (Collins, et al., J Med Chem. (2002) 45(10):1963-6; Schultz, et al., Genes Dev (2000) 14(22):2831-8; Sparrow, et al., J Biol Chem (2002) 277(12): 10021-7). No non-steroidal compounds have so far been described which show selectivity regarding the induction of ABC transporter genes without simultaneous induction of lipogenic genes like FAS and SREBP-1c (Kaneko et al. (2003) J Biol Chem (epub July 7).

[0010] It is thus an object of the invention to provide for compounds which by means of binding the LXR receptor act as partial agonists of said receptor with a selective property regarding the upregulation of genes like the ABC transporters in macrophages and/or other cell types and a stronlgy reduced liability to increase the expression of genes involved in triglyceride synthetic pathways (like FAS and SREBP-1c). These compounds should show utility for treating

diseases or conditions which are due to or influenced by said nuclear receptor.

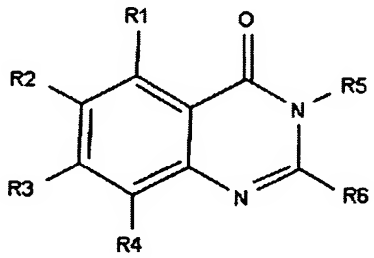
[0011] It is further an object of the invention to provide for compounds that may be used for the manufacture of a medicament for the treatment of cholesterol associated conditions or diseases. It is still a further object of the invention to provide for compounds that lower serum cholesterol and/or increase High Density Lipoproteins (HDL) and/or decrease Low Density Lipoproteins (LDL). It is also an object of the invention to provide for compounds that may be used for the treatment of lipid disorders including hypercholesterolemia, atherosclerosis, Alzheimer's disease, skin disorders, inflammation, obesity and diabetes.

[0012] The present invention provides, inter alia, novel LXR nuclear receptor protein binding compounds according to the general formula (I) shown below. Said compounds are also binders of mammalian homologues of said receptor. Further the object of the invention was solved by providing for amongst the LXR nuclear receptor protein binding compounds according to the general formula (I) such compounds which act as partial agonists or mixed agonists / antagonists of the human LXR receptor or a mammalian homologue thereof. Further the object of the invention was solved by providing for amongst the LXR receptor protein binding compounds according to the general formula (I) such compounds which act as partial agonists of the human LXR receptor resulting therefore in the induction of ABC transporter proteins such as ABCA1 or ABCG1 in cell types such as macrophages but lacking a strong potential to induce genes involved in triglyceride synthetic pathways such as fatty acid synthase (FAS) or SREBP1c.

[0013] The invention provides for LXR agonists that may be used for the manufacture of a medicament for the treatment of cholesterol associated conditions or diseases. In a preferred embodiment compounds are provided that lower serum cholesterol and/or increase High Density lipoproteins (HDL) and/or decrease Low Density Lipoproteins (LDL). Also compounds are provided that may be used for the treatment of lipid disorders including hypercholesterolemia, atherosclerosis, Alzheimer's disease, skin disorders, inflammation, obesity and diabetes.

[0014] The invention provides for a compound of the formula (I), or pharmaceutical acceptable salts or solvates thereof, hereinafter also referred to as the "compounds according to the invention" including particular and preferred embodiments thereof.

Formula (I)

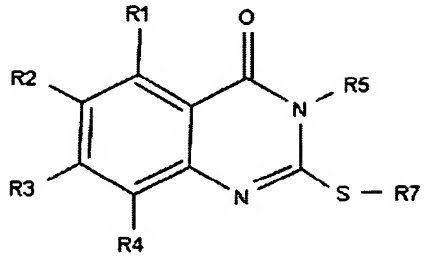


The compounds of the invention can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

[0015] In one embodiment of the invention in formula (I) above, R_1, R_2, R_3, R_4, - independent from each other - H, halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or substituted or unsubstituted phenyl, for example a biphenyl,
R_5 is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl
R_6 is H, a secondary or a tertiary amine, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl

[0016] Formula (II) shows another embodiment of the invention wherein

Formula (II)

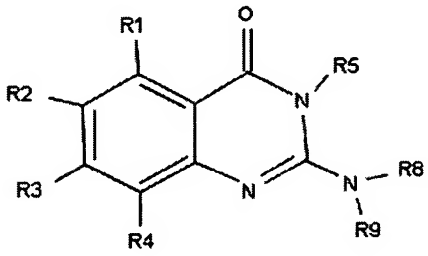


(II)

wherein R_7 is C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl

[0017] Another embodiment of the invention is described in formula (III)

Formula (III)



(III)

R_1, R_2, R_3, R_4, is H, halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl,

R_5 in formula (III) is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl,

R_8 in formula (III) is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl) amino or phenyl,

R_9 in formula (III) is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl) amino or phenyl, or

R_8 and R_9 in formula (III) are taken together with the N in formula (III) to form a ring of the following types:

C_3 to C_8 mono, di- or tri- heteroatom-substituted cycloalkyl such as but not limited to piperidino, morpholino, thiomorpholino, piperazino, or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated

derivatives thereof

C_4 to C_{10} mono, di- or tri- heteroatom-substituted bi- or tricycloalkyl or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof

C_3 to C_8 mono, di- or tri- heteroatom-substituted heteroaryl such as but not limited to pyrrolo, pyrazolo, oxazolo, thiazolo, pyridino, pyridazino, pyrimidino, pyrazino, triazino, indolo, quinolino, quinazolino or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof

[0018] In a preferred embodiment of the invention according to formula (III)

R_1 and R_3 are preferrably H,

R_2 and R_4 are preferrably H, or a halogen such as iodo, bromo, chloro or fluoro or hydroxy methyl, trifluoromethyl, methoxy, amino, alkylated amino, or nitro R_5 is H, C_1 to C_8 alkyl, preferrably isopropyl, vinyl, 2-isobutyl, or cyclohexyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl,

R_8 and R_9 in formula (III) are taken together with the N in formula (III) to form a ring of the following types:

C_3 to C_8 mono, di- or tri- heteroatom-substituted cycloalkyl such as but not limited to piperidino, morpholino, thiomorpholino, piperazino, or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof, preferrably a 4-aryl- or 4-heteroaryl- or 4-alkyl-substituted piperazino or a 4-alkyl-substituted piperidino

C_4 to C_{10} mono, di- or tri- heteroatom-substituted bi- or tricycloalkyl or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof

C_3 to C_8 mono, di- or tri- heteroatom-substituted heteroaryl such as but not limited to pyrrolo, pyrazolo, oxazolo, thiazolo, pyridino, pyridazino, pyrimidino, pyrazino, triazino, indolo, quinolino, quinazolino or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof

[0019] In another preferred embodiment of the invention according to formula (III)

R_1 and R_3 are preferrably H,

R_2 and R_4 are preferrably H, or a halogen such as iodo, bromo, chloro or fluoro or hydroxy methyl, trifluoromethyl, methoxy, amino, alkylated amino, or nitro

R_5 is H, C_1 to C_8 alkyl, preferrably isopropyl, vinyl, 2-isobutyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl,

R_8 is a C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, preferrably benzyl or (furan-2-yl)-methyl or (thiophen-2-yl)-methyl

and R_9 in formula is C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, preferably, however, (ethyl)-propion-1-yl

[0020] The symbol "H" denotes a hydrogen atom.

[0021] The term "C_1 to C_7 acyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, benzoyl and the like. Preferred acyl groups are acetyl and benzoyl.

[0022] The term "C_1 to C_7 substituted acyl" denotes the acyl group substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, C_1 to C_6 alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_4 alkylthio or C_1 to C_4 alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and pref-

erably once or twice, with the same or with different substituents.

[0023] The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted) amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl)amino or phenyl, wherein the phenyl is substituted or unsubstituted, such that, for example, a biphenyl results.

[0024] Examples of the term "substituted phenyl" includes a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2, 3 or 4-nitrophenyl; a cyanophenyl group, for example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl, 2, 3 or 4-(n-propyl) phenyl and the like; a mono or di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3 or 4-(isopropoxy)phenyl, 2, 3 or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl) phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl) phenyl or (protected aminomethyl)phenyl such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

[0025] The term "heteroaryl" means a heterocyclic aromatic derivative which is a five-membered or six-membered ring system having from 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. Examples of heteroaryls include pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, thiopheno, oxazolo, isoxazolo, phthalimido, thiazolo and the like.

[0026] The term "substituted heteroaryl" means the above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted) amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups.

[0027] The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties either on the same ring or on different rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino.

[0028] Examples of the term "substituted naphthyl" includes a mono or di(halo)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl, 2, 5-dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-bromonaphthyl, 3, 4-dibromonaphthyl, 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-fluoronaphthyl and the like; a mono or di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-hydroxy derivatives thereof and the like; a nitronaphthyl group such as 3- or 4-nitronaphthyl; a cyanonaphthyl group, for example, 1, 2, 3, 4, 5, 6, 7 or 8-cyanonaphthyl; a mono- or di(alkyl)naphthyl group such as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, 1, 2, 4-dimethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropyl)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(n-propyl)naphthyl and the like; a mono or di(alkoxy)naphthyl group, for example, 2, 6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(t-butoxy)naphthyl, 3-ethoxy-4-methoxynaphthyl and the like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a mono-or dicarboxynaphthyl or (protected carboxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-carboxynaphthyl or 2, 4-di(-protected carboxy)naphthyl; a mono-or di(hydroxymethyl)naphthyl or (protected hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(protected hydroxymethyl)naphthyl or 3, 4-di(hydroxymethyl)naphthyl; a mono- or di(amino)naphthyl or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(amino)

naphthyl or 2, 4-(protected amino)-naphthyl, a mono- or di(aminomethyl)naphthyl or (protected aminomethyl)naphthyl such as 2, 3, or 4-(aminomethyl)naphthyl or 2, 4-(protected aminomethyl)-naphthyl; or a mono- or di-(N-methylsulfonylamino) naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(N-methylsulfonylamino)naphthyl. Also, the term "substituted naphthyl" represents disubstituted naphthyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-hydroxynaphth-2-yl, 2-methoxy-4-bromonaphth-1-yl, 4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl, 3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

[0029] The term "C_1 to C_8 alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl , n-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 2-methyl-1hexyl, 2-methyl-2hexyl, 2-methyl-3-hexyl, n-octyl and the like.

[0030] The term "C_2 to C_6 alkenyl" denotes such radicals as propenyl or butenyl.

[0031] Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, amino, methylamino, aminomethyl, dimethylamino, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1- iodoethyl, 2-iodoethyl, 1-chloropropyl, 2-chloropropyl, 3- chloropropyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1- iodopropyl, 2-iodopropyl, 3-iodopropyl, 2-aminoethyl, 1- aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

[0032] The term "C_1 to C_8 substituted alkyl" denotes that the above C_1 to C_8 alkyl groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, C_3 to C_7 cycloalkyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_4 alkylthio or C_1 to C_4 alkylsulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

[0033] The term "C_7 to C_{12} phenylalkyl" denotes a C_1 to C_6 alkyl group substituted at any position by a phenyl, substituted phenyl, heteroaryl or substituted heteroaryl. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like. Preferred C_7 to C_{12} phenylalkyl groups are the benzyl and the phenylethyl groups.

The term "C_7 to C_{12} substituted phenylalkyl" denotes a C_7 to C_{12} phenylalkyl group substituted on the C_1 to C_6 alkyl portion with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted) amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-(C_1 to C_6 alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl) carboxamide, protected N-(C_1 to C_6 alkyl) carboxamide, N, N-di (C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C_2 to C_7 alkylene or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

[0034] Examples of the term "C_7 to C_{12} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)n-hexyl, 2-(5-cyano-3-methoxyphenyl)n-pentyl, 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)- 3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

[0035] The term "heterocycle" or "heterocyclic ring" denotes optionally substituted five-membered to eight-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered to eight-membered rings may be saturated, fully unsaturated or partially unsaturated, with fully saturated rings being preferred. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl, 2-amino-imidazoyl, tetrahydrofurano, pyrrolo, tetrahydrothiophen-yl, hexylmethyl-

eneimino and heptylmethyleneimino.

[0036] The term "substituted heterocycle" or "substituted heterocyclic ring" means the above-described heterocyclic ring is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl) sulfonyl)amino, N-(phenylsulfonyl)amino, heterocycle or substituted heterocycle groups.

[0037] The term "C_1 to C_8 alkoxy" as used herein denotes groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred alkoxy is methoxy. The term "C_1 to C_8 substituted alkoxy" means the alkyl portion of the alkoxy can be substituted in the same manner as in relation to C_1 to C_8 substituted alkyl.

[0038] The term "C_1 to C_8 aminoacyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, octanoyl, benzoyl and the like.

[0039] The term "C_1 to C_8 substituted aminoacyl" denotes the acyl group substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, C_1 to C_{12} alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl) carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N,N-di(C_1 to C_{12} alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_{10} alkylthio or C_1 to C_{10} alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

[0040] Examples of C_1 to C_8 substituted acyl groups include 4-phenylbutyroyl, 3-phenylbutyroyl, 3-phenylpropanoyl, 2- cyclohexanylacetyl, cyclohexanecarbonyl, 2-furanoyl and 3-dimethylaminobenzoyl.

[0041] This invention also provides a pharmaceutical composition comprising an effective amount of a compound according to the invention. Such pharmaceuticals compositions can be administered by various routes, for example oral, subcutaneous, intramuscular, intravenous or intracerebral. The preferred route of administration would be oral at daily doses of the compound for adult human treatment of about 0.01-5000 mg, preferably 1-1500 mg per day. The appropriate dose may be administered in a single dose or as divided doses presented at appropriate intervals for example as two, three four or more subdoses per day.

[0042] For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

[0043] A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

[0044] In powders, the carrier is generally a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0045] For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

[0046] Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient, preferably comprising (especially consisting of) one or more of the compounds according to this invention. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

[0047] The pharmaceutical compositions can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

[0048] Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration.

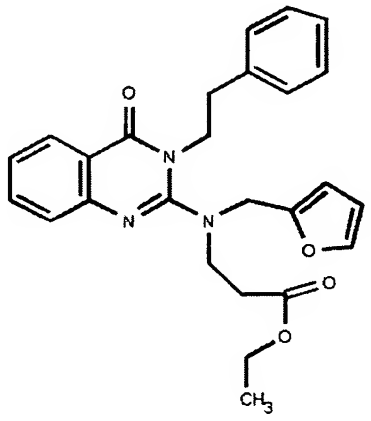
[0049] Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

[0050] In a preferred embodiment of the invention in the compounds claimed, or the pharmaceutical acceptable salts or solvates thereof, R_1, R_3 and R_4 are H, R_2 is halogen and preferably iodine over bromine and chlorine and R_5 is H,

C_1 to C_8 alkyl or C_1 to C_8 substituted alkyl.

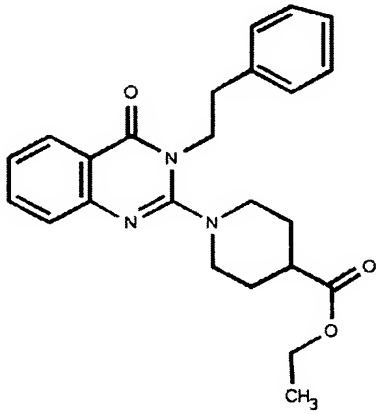
[0051] For the six preferred compounds as shown in formulae (XIII), (XII), (X), (IX), (VII), and (IV) below it was demonstrated that these compounds may act as a full or partial agonist of LXR

Formula (XIII); MOLNAME LN7181



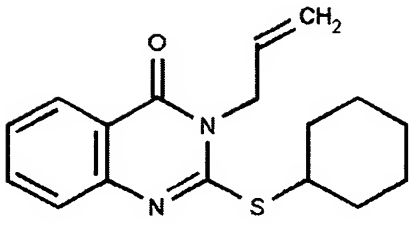
(XIII)

Formula (XII); MOLNAME LN7179



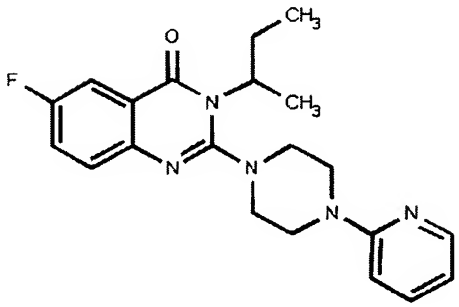
(XII)

Formula (X); MOLNAME LN7172



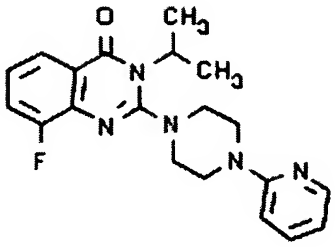
(X)

Formula (IX); MOLNAME LN6672



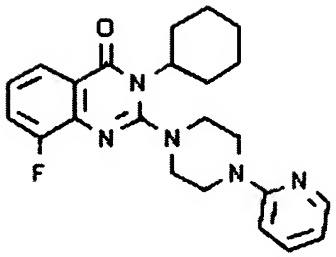
(IX)

Formula (VII); MOLNAME LN7031



(VII)

Formula (IV); MOLNAME LN7033

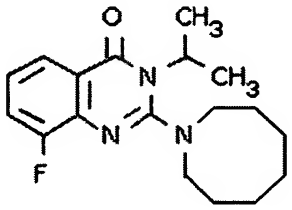


(IV)

[0052] It has also been found that the compound according to formula (IV) (MOLNAME LN7033) to be active as partial agonist of the LXR human nuclear receptors with a selective upregulation of the target genes ABCA1 and ABCG1 in THP-1 cells compared to FAS and SREBP-1c in HepG2 cells (see also Fig. 8A and 8B).

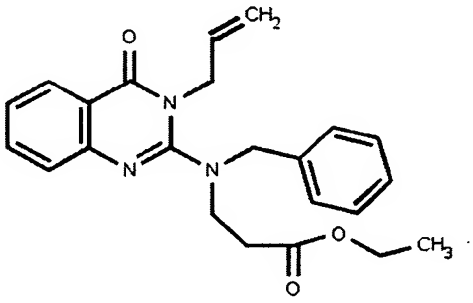
[0053] Furthermore, the present invention includes compounds of the following formula:

Formula (V), MOLNAME LN7025



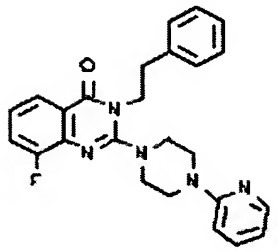
(V)

Formula (VI), MOLNAME LN7184



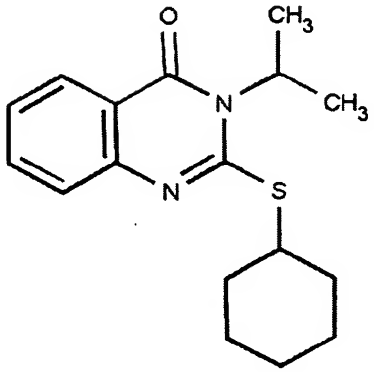
(VI)

Formula (VIII); MOLNAME LN7032



(VIII)

Formula (XI); MOLNAME LN7174



(XI)

[0054] In particular the invention relates to a compound as described above wherein said compounds is capable of binding the LXR receptor protein or a portion thereof encoded by a nucleic acid according to SEQ ID NO:1 or NO:2 (Fig. 3) or a mammalian homologue thereof. This compound can bind to the LXR receptor protein or a portion thereof in a mixture comprising 10-200 ng of LXR receptor protein, a fusion protein containing LXR or a portion thereof, preferably the ligand binding domain, fused to a Tag, 5-100 mM Tris/HCl at pH 6,8-8,3; 60-1000 mM KCl; 0-20 mM MgCl2; 100-1000ng/μl BSA in a total volume of preferably about 25 μl).

[0055] A mammalian receptor protein homologue of the protein encoded by a nucleic acid according to SEQ ID NO: 1 or 2, as used herein is a protein that performs substantially the same task as LXR does in humans and shares at least 40% sequence identity at the amino acid level, preferably over 50 % sequence identity at the amino acid level more preferably over 65 % sequence identity at the amino acid level, even more preferably over 75 % sequence identity at the amino acid level and most preferably over 85 % sequence identity at the amino acid level.

[0056] The invention in particular concerns a method for prevention or treatment of a LXR receptor protein or LXR receptor protein homologue mediated disease or condition in a mammal comprising administration of a therapeutically effective amount of a compound according to the invention wherein the prevention or treatment is directly or indirectly accomplished through the binding of a compound according to the invention to the LXR receptor protein or to the LXR receptor protein homologue.

[0057] The term mediated herein means that the physiological pathway in which the LXR receptor protein acts is either directly or indirectly involved in the disease or condition to be treated or prevented. In the case where it is indirectly involved it could be that, e.g. modulating the activity of LXR by a compound according to the invention influences a parameter which has a beneficial effect on a disease or a condition. One such example is that modulation of LXR activity leads to decreased levels of serum cholesterol or certain lipoproteins which in turn have a beneficial effect on the prevention and treatment of atherosclerosis. Herein a condition is a physiological or phenotypic state which is desirably altered. One such example would be obesity which is not necessarily medically harmful but nonetheless a non desirable phenotypic condition. In a preferred embodiment of the invention the method for prevention or treatment of a LXR receptor protein mediated disease or condition is applied to a human. This may be male or female.

[0058] Pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 μg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. Preferably, in most cases, doses is from about 100 μg/kg to about 5 mg/kg body weight, daily.

[0059] For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of active agent will be 0,1 mg/kg to 10 mg/kg and typically around 1 mg/kg.

[0060] By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cholesterol-reducing amount, a cholesterol absorption blocking amount, a protein and/or carbohydrate digestion-blocking amount and/or a de novo cholesterol biosynthesis-blocking amount of a compound according to the invention.

[0061] Likewise the invention concerns a method of treating in mammal a disease which is correlated with abnormal cholesterol, triglyceride, or bile acid levels or deposits comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to the invention.

[0062] Accordingly, the compounds according to the invention may also be used in a method of prevention or treatment of mammalian atherosclerosis, gallstone disease, lipid disorders, Alzheimer's disease, skin disorders, inflammation, obesity or cardiovascular disorders such as coronary heart disease or stroke.

[0063] The invention further concerns a method of blocking in a mammal the cholesterol absorption in the intestine in need of such blocking comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to the invention. The invention may also be used to treat obesity in humans.

[0064] The Liver X Receptor alpha is a prototypical type 2 nuclear receptor meaning that it activates genes upon binding to the promoter region of target genes in a heterodimeric fashion with Retinoid X Receptor. The relevant physiological ligands of LXR are oxysterols. The compounds have been demonstrated to have a high binding efficacy (binding coefficients measured as EC50 in the range of 1-5 μM) as well as agonistic and/or partial agonistic properties. Consequently they may be applied to regulate genes that participate in bile acid, cholesterol and fatty acid homeostasis as well as other downstream regulated genes. Examples of such genes are but are not limited to lipid absorption, cholesterol biosynthesis, cholesterol transport or binding, bile acid transport or binding, proteolysis, amino acid metabolism, glucose biosynthesis, protein translation, electron transport, and hepatic fatty acid metabolism. LXR often functions in vivo as a heterodimer with the Retinoid X Receptor. Published non-steroidal LXR agonists such as the "Tularik" compound "TO901317" (see figure 5) are known to influence the regulation of various liver genes. Genes found to be regulated by T0901317 can be found in figure 6. Thus, the invention also concerns a method of modulating a gene whose expression is regulated by the LXR receptor in a mammal comprising administration of a therapeutically effective amount of a compound according to the invention to said mammal.

[0065] A number of direct and indirect LXR target genes have been described whose regulated expression contributes to cholesterol homeostasis and lipogenesis. In this respect the direct regulation of Cyp7A, which was shown to be a direct target gene of LXR at least in the rodent lineage is an important aspect of cholesterol removal by increased metabolism of bile acids (Lehmann et al., J Biol.Chem. 272 (6) 3137-3140; 1007). Gupta et al. (Biochem. Biophys Res. Com, 293; 338-343, 2002) showed that LXR α regulation of Cyp7A is dominant over FXR inhibitory effects on Cyp7A transcription.

[0066] A key transcription factor that was also shown to be a direct target gene for the LXR receptor is SREBP-1 C (Repa et al., Genes and Development, 14:2819-2830; 2000: Yoshikawa et al.; Mol.Cell.Biol.21 (9) 2991-3000, 2001). SREBP-1 C itself activates transcription of genes involved in cholesterol and fatty acid synthesis in liver but also other mammalian tissues. Some of the SREBP1c target genes involved in lipogenesis like FAS and SCD have shown to be additionally direct targets of the LXR receptors (Joseph et al.; J Biol Chem. 2002 Mar 29;277(13):11019-25; Liang et al., J Biol Chem. 2002 Mar 15;277(11):9520-8.).

[0067] A primary limitation for the applicability of LXR agonists as e.g. anti-atherosclerotic drugs comes from the observation that compounds with full agonistic activity, e.g. T0901317, not only elevate HDL cholesterol levels but do also increase plasma triglyceride levels in mice (Schultz et al., 2000 Genes Dev. 14:2831-8.). Concommitantly, not only genes that are involved in cholesterol efflux such as the cholesterol transporter ABCA1 (Venkateswaran et al., 2000 PNAS. 97:12097-102.), ABCG1 as well as the lipid binding protein Apoliprotein E (Laffite et al. 2001 PNAS 98: 507-512) are induced by full LXR agonists, but also genes involved in lipogenesis, including the fatty acid synthase FAS (Joseph et al 2002 J Biol Chem. 277:11019-11025), and SREB P-1c (Yoshikawa et al., 2001 Mol Cell Biol. 21: 2991-3000). Elevation of serum triglyceride levels is an indendent risk factor for atherosclerosis (for review see Miller, 1999). Thus, LXR activity needs to be selectively modulated for therapeutic benefit. In particular, compounds need to be found that stimulate reverse cholesterol transport, but do not significantly increase trigclyceride levels.

[0068] Another gene that has been shown to be directly regulated by LXRs is the LPL gene, that codes for a key enzyme that is responsible for the hydrolysis of triglycerides in circulating lipoprotein, releasing free fatty acids to peripheral tissues. (Zhang et al. J Biol Chem. 2001 Nov 16;276(46):43018-24.) This enzyme is believed to promote

uptake of HDL cholesterol in liver, thereby promoting reverse cholesterol transport. A similar functional involvement in HDL clearance is described for the CETP gene product that facilitated the transfer of HDL cholesterol esters from plasma to the liver. LXR response elements were found in the CETP promoter and direct activation of this gene by LXR was demonstrated (Luo and Tall; J Clin Invest. 2000 Feb;105(4):513-20.).

[0069] The regulated transport of cholesterol through biological membranes is an important mechanism in order to maintain cholesterol homeostasis. A pivotal role in these processes in multiple tissues like e.g. macrophages and intestinal mucosa cells is maintained by the ATP-binding cassette transporter proteins (ABC). ABCA1 and ABCG1 were identified as direct LXR target genes (Costet et al.; J Biol Chem. 2000 Sep 8;275(36):28240-5) that mediate cholesterol efflux and prevent thereby e.g. generation of artherogenic plaques in macrophages (Singaraja et al. J Clin Invest. 2002 Jul;110(1):35-42). Other ABC transporters like ABCG5 and ABCG8, primarily expressed in hepatocytes and enterocytes have also been reported to be directly responsive to LXR agonists (Repa et al., J Biol Chem. 2002 May 24;277(21):18793-800. Kennedy et al., J Biol Chem. 2001 Oct 19;276(42):39438-47) and mediate the secretion of sterols from the liver and efflux of dietary sterols from the gut. Apolipoproteins E, C-I, C-II, and C-IV, that fulfill important roles in lipoprotein/lipid homeostasis have also been shown to be direct targets of the LXR receptor (Laffitte et al., Proc Natl Acad Sci U S A. 2001 Jan 16;98(2):507-12; Mak et al.; J Biol Chem. 2002 May 24 [epub ahead of print]). These proteins have been found to be crucial components of chylomicrons, VLDL, IDL, and HDL and are among other things associated with hypertriglyceridemia and arteriosclerosis.

[0070] Recently the LXRα itself was shown to be regulated by both LXR receptors in human cell types including macrophages suggesting an autoregulatory amplification event in the response to LXR ligands which could e.g. lead to an enhanced stimulation of LXR target genes like e.g. ABCA1 (Bolten et al.; Mol Endocrinol. 2002 Mar;16(3):506-14.; Laffitte et al., Mol Cell Biol. 2001 Nov;21 (22):7558-68; Whitney et al.; J Biol Chem. 2001 Nov 23;276(47):43509-15).

[0071] Besides the important function of LXR receptors in tissues like liver and macrophages it has recently been reported that that stimulation of epidermal differentiation is mediated by Liver X receptors in murine epidermis. Differentiation maker genes like involucrin, loricin and profilaggrin have been shown to be upregulated upon LXR ligand treatment (Kömüves et al.; J Invest Dermatol. 2002 Jan;118(1):25-34.).

[0072] Another recent report describes the regulation of cholesterol homeostasis (primarily the regulation of ABCA1, ABCG1 and SREBP-1C) by the LXR receptors in the central nervous system suggesting that LXRs may prove benefical in the treatment of CNS diseases such as Alzheimer's and Niemann-Pick disease that are known to be accompanied by dysregulation of cholesterol balance (Whitney et al.; Mol Endocrinol. 2002 Jun;16(6):1378-85).

[0073] Activation of LXR by an agonist improves glucose tolerance in a murine model of diet-induced obesity and insulin resistance. Gene expression analysis in LXR agonist-treated mice reveals coordinate regulation of genes involved in glucose metabolism in liver and adipose tissue, e.g. the down-regulation of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1), phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase expression and induction of glucokinase in liver. In adipose tissue, activation of LXR led to the transcriptional induction of the insulin-sensitive glucose transporter, GLUT4. LXR agonist may limit hepatic glucose output and improve peripheral glucose uptake (Laffitte et al. (2003) PNAS 100:5419-24).

[0074] Therefore one other important embodiment of the invention concerns methods that enhances or suppresses amongst other today yet unknown LXR target genes the above mentioned genes and the associated biological processes and pathways through LXR compounds that are subject of this invention.

[0075] The compounds according to the invention may be used as medicaments, in particular for the manufacture of a medicament for the prevention or treatment of a LXR receptor protein or LXR receptor protein homologue mediated disease or condition in a mammal wherein the prevention or treatment is directly or indirectly accomplished through the binding of the compound according to the invention to the LXR receptor protein or LXR receptor protein homologue. These pharmaceutical compositions contain 0,1 % to 99,5 % of the compound according to the invention, more particularly 0,5 % to 90 % of the compound according to the invention in combination with a pharmaceutically acceptable carrier.

[0076] The invention concerns also the use of a compound according to the invention for the manufacture of a medicament for the prevention or treatment of a LXR receptor protein mediated disease or condition wherein the mammal described above is a human. The medicament may be used for regulating the cholesterol transport system, for regulating levels of cholesterol, triglyceride, and/or bile acid in a mammal preferentially a human by activating the LXR receptor. The medicament may be used for the treatment of atherosclerosis, gallstone disease, lipid disorders, Alzheimer's disease, skin disorders, obesity or a cardiovascular disorder.

[0077] The invention further concerns the use of a compound according to the invention for the manufacture of a medicament capable for blocking in a mammal, preferentially in a human the cholesterol absorption in the intestine. Further the claimed compound may be used for the manufacture of a medicament for treating obesity in humans and for modulating a gene whose expression is regulated by the LXR receptor (see details above and figures).

EXAMPLES

EXAMPLE 1

[0078] In vitro screening for compounds which influence LXR binding to coactivators.

[0079] For screening purposes a GST and 6 x His fusion of the LBD (from amino acids 155 of hLXRalpha to 447) of human LXRalpha is constructed by first cloning a Gateway cassette (Invitrogen) in frame into the Sma I site of the pAGGHLT Polylinker (Pharmingen). Then a PCR fragment specifically amplified from human liver cDNA is cloned into the resulting pACGHLT-GW following the manufacturers instructions for Gateway cloning (Invitrogen) to yield pACGHLT-GW-hLXRalphaLBD.

Primers used for Amplification are:

GGGGACAAGTTTGTACAAAAAAGCAGGCTCGCTTCGCAAATGCCGTCAG

and

GGGGACCACTTTGTACAAGAAAGCTGGGTCCCCTTCTCAGTCTGTTCCACTT .

100 % sequence integrity of all recombinant products is verified by sequencing. Recombinant Baculovirus is constructed from pACGHLT-GW-hLXRalphaLBD using the Pharmingen Baculovirus Expression vector system according to instructions of the manufacturer. Monolayer cultures of SF9 cells are infected by the virus as recommended by Pharmingen or 200ml cultures of 1 $x10^6$ cells/ml grown in 2 liter Erlenmeyer flasks on an orbital shaker at 30 rpm are infected by 10ml of same virus stock. In both cases cells are harvested 3 days after infection. All cell growth is performed in Gibco SF900 II with Glutamine (Invitrogen) medium without serum supplementation at 28°C. Since SF9 cells contain significant amounts of endogenous GST, purification is performed via His and not via GST affinity chromatography. To this end instructions of Pharmingen for purification of recombinant His tagged proteins from SF9 cells are followed with the following modifications: All detergents are omitted from the buffers and cells were lysed on ice by 5 subsequent sonication pulses using a sonicator needle at maximum power. All eluates are dialyzed against 20 mM Tris/HCl pH 6,8, 300 mM KCl; 5 mM $MgCl_2$; 1 mM DTT; 0,2 mM PMSF; 10% Glycerol. A typical dialyzed eluate fraction contains the fusion protein at a purity of more than 80%. Total protein concentration is 0,1-0,3 mg/ml.

For E. coli expression of a NR coactivator, pDest17-hTif2BD expressing a NR interaction domain from amino acids 548-878 of human Tif2 (Acc. No: XM_011633 RefSeq) tagged by 6 N-terminal His residues is constructed. Therefore, a PCR fragment specifically amplified from human liver cDNA is subcloned into pDest 17 (Invitrogen) following the manufacturers instructions for Gateway cloning (Invitrogen).Primers used for Amplification are:

GGGGACAAGTTTGTACAAAAAAGCAGGCTCGTTAGGGTCATCGTTGGCTTCACC

and

GGGGACCACTTTGTACAAGAAAGCTGGGTCTCAAAGTTGCCCTGGTCGTGGGT
TA

For E. coli expression plasmid DNA is transformed into chemically competent E. coli BL21 (Invitrogen, USA) and cells are grown to an OD600 of 0.4-0.7 before expression was induced by addition of 0,5 mM IPTG according instructions of the manufacturer (Invitrogen). After induction for 8 hours at 30°C cells are harvested by centrifugation for 10 minutes at 5000 x g. Fusion proteins are affinity purified using Ni-NTA Agarose (QIAGEN) according to the instructions of the manufacturer. Recombinant Tif2 construct is dialyzed against 20 mM Tris/HCL pH 7.9; 60 mM KCl; 5 mM $MgCl_2$; 1 mM DTT, 0,2 mM PMSF; 10% glycerol. A typical dialyzed eluate fraction contains the fusion protein at a purity of more than 80%. Total protein concentration is 0,1-0,3 mg/ml.

The TIF2 fragment is subsequently biotinylated by addition of 5-40µl/ml Tif2 fraction of a Biotinamidocaproate N-Hydroxysuccinimide-ester (Sigma) solution (20 mg/ml in DMSO). Overhead rotating samples are incubated for 2 hours at room temperature. Unincorporated label is then separated using G25 Gel filtration chromatography (Pharmacia Biotech, Sweden). Protein containing fractions from the column are pooled and tested for activity in the assay as

described below.

[0080] For screening of compound libraries as provided for by the methods shown below in the examples for substances which influence the LXR/Tif 2 interaction, the Perkin Elmer LANCE technology is applied. This method relies on the binding dependent energy transfer from a donor to an acceptor fluorophore attached to the binding partners of interest. For ease of handling and reduction of background from compound fluorescence LANCE technology makes use of generic fluorophore labels and time resoved detection (for detailed description see Hemmilä I, Blomberg K and Hurskainen P, Time-resolved resonance energy transfer (TR-FRET) principle in LANCE, Abstract of Papers Presented at the 3 rd Annual Conference of the Society for Biomolecular Screening, Sep., California (1997))
For screening, 20-200 ng of biotinylated Tif 2 fragment and 10-200 ng of GST-LXR fragment are combined with 0.5-2 nM LANCE Eu-(W1024) labelled anti-GST antibody (Perkin Elmer) and 0,1-0,5µg of highly fluorescent APC-labelled streptavidin (Perkin Elmer, AD0059) in the presence of 50µM of individual compounds to be screened in a total volume of 25 µl of 20 mM Tris /HCl pH 6,8; 300 mM KCl; 5 mM MgCl2; 100-1000 ng/µl/ BSA DMSO content of the samples is kept below 4%. Samples are incubated for a minimum of 60 minutes in the dark at room temperature in FIA-Plates black 384well med. binding (Greiner).

[0081] The LANCE signal is detected by a Perkin Elmer VICTOR2V™ Multilabel Counter applying the detection parameters listed in Fig. 2. The results are visualized by plotting the ratio between the emitted light at 665 nm and at 615 nm. For every batch of recombinant proteins amount of proteins, including BSA and labeling reagents giving the most sensitive detection of hits is determined individually by analysis of dose response curves for 22R Hydroxycholesterol and TO 901317

EXAMPLE 2

[0082] Experimental procedure for the preparation of the compounds according to the invention.

o-AZIDOBENZOIC ACID SYNTHESIS (2)

[0083] The anthranilic acid (1, 1 eq., 0.5-1 M) is suspended in 6 M HCl, containing enough AcOH (0-20% dependent upon the anthranilic acid) to facilitate dissolution of the anthranilic acid and/or the intermediate diazonium salt, and cooled to 0 °C. $NaNO_2$ (1.1 eq., 1.3-2.5 M) dissolved in H_2O is added to the anthranilic acid solution at a rate such that the temperature of the reaction solution remains below 5 °C. The resulting homogeneous solution of the diazonium salt is slowly filtered through a sintered glass funnel into a solution of NaN_3 (1.1 eq., 0.7-1.1 M) and NaOAc (12 eq.) in H_2O. The reaction mixture is stirred/shaken for 30-60 min following cessation of vigorous N_2 evolution. Following acidification of the reaction mixture to pH 1 with concentrated HCl, the mixture was cooled to 0 °C to encourage complete precipitation of the o-azidobenzoic acid. The precipitate is collected by filtration and washed with 6 M HCl (2x) and H_2O (2x). The *o*-azidobenzoic acid product (2) is dried *in vacuo* (500 mtorr, 30°C).

ACYLATION OF HYDROXYMETHYL RESIN (4)

[0084] To hydroxymethyl resin (1.0 eq., 1.3 mmol/g) and the *o*-azidobenzoic acid (1, 2.5 eq.) is added DMF (to give 400 mM *o*-azidobenzoic acid ,1), $CsCO_3$ (2.0 eq.) and KI (2.0 eq.). Following agitation of the reaction mixture for 36-48 h, the resin-bound *o*-azidobenzoic acid (4) is washed with MeOH (2 cycles), CH_2Cl_2 (3 cycles), MeOH (3 cycles), DMF (3 cycles), MeOH (3 cycles) and CH_2Cl_2 (3 cycles), and dried *in vacuo.*

AZA-WITTIG FORMATION (5)

[0085] To the resin-bound o-azidobenzoic acid (4,1.0 eq.) is added a solution of PPh_3 (THF, 500 mM, 5.0 eq.). After 6 h, the resin is washed with 3 cycles of the following: THF (3 cycles), toluene (3 cycles), CH_2Cl_2 (3 cycles) and hexanes (3 cycles). Followed by drying *in vacuo* to afford resin bound iminophosphorane (5)

CARBODIIMIDE FORMATION (6)

[0086] To the resin-bound iminophosphorane (5, 1 eq.) is added isocyanate (9 , 5 eq., 450 mM) dissolved in $ClCH_2CH_2Cl$. The compounds are shaken at ambient temperature for 16 h, washed with 3 cycles of the following: THF (3 cycles), toluene (3 cycles), CH_2Cl_2 (3 cycles) and hexanes (3 cycles), and dried *in vacuo* to afford carbodiimide (6).

GUANIDINE FORMATION / CYCLIZATION

[0087] To the carbodiimide functionalized resin (6) is added secondary amine (10, 0.6 eq., 500 mM) dissolved in

$ClCH_2CH_2Cl$. The reaction mixture is heated to 50 °C in an incubator for 12-72 h to afford 2-aminoquinazoline (8).

[0088] All of the final products are analyzed using an Evaporative Light Scattering Detector (ELSD) detection to determine purity.

EXAMPLE 3

[0089] This example illustrates that compounds according to the invention (experiments shown were done with MOLSTRUCTURE LN0000007033 (see formulas (9)) activate luciferase reporter gene expression in a dose dependent manner mediated through GAL4-LXRa-LBD or GAL4-LXRb-LBD constructs in HEK293 cells. LN0000007033 does activate LXR beta LBD truct mediated luciferase activity much stronger than with LXR alpha construct which is in contrast to the similar activation of both LXR alpha and LXR beta LBD containing constructs with T0901317 (see Fig. 7).

[0090] HEK293 cells are grown in 96 well plates and co-transfected with pFR-luc (Stratagene) and pCMV-BD-LXRa-LBD or pCMV-BD-LXRb-LBD (each 100 ng of plasmid DNA per well). Transfection is carried using Lipfectamine 2000 (Gibco-BRL) according to the manufacturers protocol. The ligand binding domains (LBD) of LXRa and LXRb are cloned into the pCMV-BD-GW (the Gateway Reading Frame Cassette B is cloned as an EcoRV fragment into SmaI site of pCMV-BD) applying the manufacturer protocols for the Gateway™ system (Invitrogen).

Luciferase reporter activity is measured in triplicates from extracts of cells after incubating cells in culture medium (DMEM [Gibco-BRL] + 10% FCS [PAA laboratories]) for 16 hours (5% CO_2, 37°C) containing 0,5% DMSO (control) or 0,5% DMSO with increasing concentrations of LN0000007033. The type of assay used here is a mammalian one hybrid (M1H) assay that is known to those skilled in the art.

[0091] Dose-dependent luciferase activities originating from pFR-luc demonstrate the relative activities of the compounds with the LXRa or LXRb LBDs in this mammalian one hybrid type approach.

EXAMPLE 4

[0092] This example shows that described compounds can increase the abundance of mRNA of LXR target genes like ABCA1 and ABCG1 in THP-1 cells which are treated with TPA or FAS and SREBP-1c in HepG2 cells as shown in Fig 8A and Fig. 8B.

[0093] THP-1 cells are seeded in 24 well plates at 3 $x10^5$ cells per well in RPMI 1640 medium containing 10 % FCS and 100 nM TPA for 24 h. HepG2 cells are seeded in poly-L-Lysine coated 24well plates at $1x10^6$ cells per well in EMEM medium containing 10 % FCS until they are appr. 60% confluent.

Before treatment with LXR compounds, the growth medium is changed to medium containing 10% charcoal/dextran-stripped FCS for 12 h. Treatment is done for 12h (THP-1 cells) and 24h (HepG2 cells), respectively, in medium containing 10% charcoal/dextran-stripped FCS (and 100 nM PMA in the case of THP-1 cells).

LXR compounds are dissolved in DMSO, with the final solvent concentration never exceeding 0.125%. All treatments are done in triplicates and experiments repeated twice. Total RNA is extracted using the Qiagen Rneasy Mini Kit and treated with DNase (DNAfree kit, Ambion). RNA is reverse transcribed with Oligo(dT) primer and real-time reverse transcription PCR (TaqMan) is performed using the ABI Prism 7900HT Sequence Detection System and reagents supplied by Applied Biosystems. mRNA steady state levels are normalised to H3 histone (H3F3A) expression levels. The sequences of forward primers, reverse primers and TaqMan probes are as follows :

FAS : CTGAGACGGAGGCCATATGCT, GCTGCCACACGCTCCTCTAG, FAM-CAGCAGTTCACGGACATGGAGCACAA-TAMRA

ABCA1 :TCCTGTGGTGTTTCTGGATGAAC, CTTGACAACACTTAGGGCACAATTC, FAM- ACCACAGGCATGGATCCCAAAGCC-TAMRA

EXAMPLE 5

[0094] LN0000007033 causes a marked increase in cholesterol export in differentated THP-1 macrophages (see Figure 9 A).

Strikingly, the compound T0901317 causes a marked increase in triyglyceride mass in HepG2 liver cells, while compounds like LN0000007033 and LN0000007025 do not cause a significant increase in triglyceride mass.

This behavior is similar to the selective transcriptional effect of compounds like LN0000007033 and LN0000007025

on the LXR target genes in HepG2 versus THP-1 cells (see Fig 8A and 8B).

[0095] Methods: Cultures of the monocyte-macrophage cell line and the hepatocytes HepG2 are obtained from the American Type tissue Culture Collection, Rockville, MD and were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum, 10 mM HEPES, 2 mM Pyruvat, 50 μM β-Mercaptoethanol (THP-1) and Minimum essential medium (Eagle) with 2 mM L-glutamine and Earle's BSS supplemented with 10% fetal bovine serum, 2 mM glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate (HepG2), respectively, at 37°C in 5% CO2.
THP-1 cells are differentiated into macrophages by addition of 100 nM Phorbol 12-Myristate 13-Acetate (PMA; Sigma P8139) and PMA included in the medium of all subsequent experiments to maintain differentiation.
For cholesterol efflux measurements and triglyceride analysis cells are seeded in 6well plates at 1.8x106 cells (THP-1) and 1x106 cells (HepG2) per well, respectively.

CHOLESTEROL EFFLUX

[0096] THP-1 cells are seeded in 6well plates at $1x10^6$ cells per well in RPMI 1640 medium containing 10 % FCS and 100 nM TPA for 72 h. After washing with PBS cells are incubated 24 h with fresh in RPMI 1640 medium containing 10 % FCS and 100 nM TPA. Cells are washed twice with PBS and RPMI 1640 medium containing 0.15% BSA and 100 nM TPA is added for further 24 h. Treatment with LXR compounds is done for 24 h in RPMI 1640 medium containing 0.15% BSA, 100 nM TPA and 40 μg/ml ApoA1 (Calbiochem # 178452). Medium is collected, centrifuged to remove cell debris and assayed for cholesterol using a commercial fluorometric kit (Molecular Probes A-12216). The remaining cellular proteins are lysed with 0.3 N NaOH and protein content measured with the Biorad Bradford reagent.

TRIGLYCERIDE ASSAY

[0097] HepG2 cells are seeded in poly-L-Lysine coated 6well plates at $1x10^6$ cells per well in EMEM medium containing 10 % FCS until they were appr. 60% confluent. Before treatment with LXR compounds growth medium is changed to medium containing 10% charcoal/dextran-stripped FCS for 12 h. Treatment is done for 24h in medium containing 10% charcoal/dextran-stripped FCS. Cells are washed twice with ice-cold PBS/0.2% BSA and twice with cold PBS and all liquid carefully removed. Triglyceride are extracted with with 1.5 ml hexane/ isopropanol = 3:2 per well with gentle shaking for 2-3 h at RT according to Pan et al. (2002) JBC 277, 4413-4421 and Goti et al. (1998) Biochem J, 332, 57-65. The extraction solution is collected, dried under vacuum and redissolved in isopropanol/ 1.5% triton. The remaining cellular proteins are lysed with 0.3 N NaOH and protein content measured with the Biorad Bradford reagent.
Triglyceride levels are measured as esterified glycerol using a commercial enzymatic colorimetric kit (Sigma 343-25P). In a preliminary assay it is checked by omitting the lipase enzyme that contribution of free glycerol is negligible.

FIGURE CAPTIONS

FIG. 1

[0098] Fig. 1 shows the synthesis of the compounds according to the invention as also described in Example 2.

FIG. 2

[0099] Fig. 2 shows the measurement parameters employed by the Wallace VICTOR2V™ Multilabel Counter which was used for measuring the EC_{50} values

FIG. 3

[0100] Shows a table with the accession numbers for the key genes

FIG. 4

[0101] Fig. 4 shows the internal molecular name used by the applicant (MOLNAME) as well as the corresponding structures of preferred compounds according to the invention. The figure further shows their respective EC_{50} values (EC50 AVG) as established according to the Example 1 in multiple experiments (see above), as well as their respective average efficacy (% activity relative to TO901317 control agonist).

FIG. 5

[0102] Figure 5 shows various known LXR ligands. The compound T0901317 is used as a reference compound here. It is apparent from their structures that the inventors have identified novel compounds which are structurally not related to these known ligands.

FIG. 6

[0103] Figure 6 shows various genes that have been found to be regulated through binding of an LXR agonist to the LXR protein.

FIG. 7

[0104] Fig 7 shows a dose dependence of LN0000007033 with LXR beta LBD containing constructs in mammalian one hybrid (M1H) type assays. The respective μM concentrations of the compounds are given on the x-axis and the relative light units (RLU) are depicted on the y-axis.

Fig. 8 A and B

[0105] Analysis of mRNA content of the indicated genes (LXRalpha, ABCA1, ABCG1, FAS and SREBP-1 c) in total RNA isolated from THP-1 cells (8A, LXRalpha, ABCA1, ABCG1) or HepG2 cells (8B, FAS and SREBP-1 c) treated for 12 or 24 hours with 10 μM on x-axis of T0901317 and LN0000007033. The relative fold induction is depicted on the y-axis and the value depicted with * for ABCG1 has to be multiplicated by a factor of 10.

Fig. 9

[0106] Analysis of relative fold increase in total cholesterol from supernatants of cultivated THP-1 cells (indicated on the y-axis) incubated with ApoA1 and with or without 10μM of the compounds T0901317, LN0000007033 and LN0000007025 as indicated on the X-axis of Fig 9A.
Analysis of relative levels of total triglyceride (TG) content in HepG2 cells (indicated on the y-axis) treated with 25μM of the indicated compounds T0901317, LN0000007033 and LN0000007025 (indicated on the x-axis).

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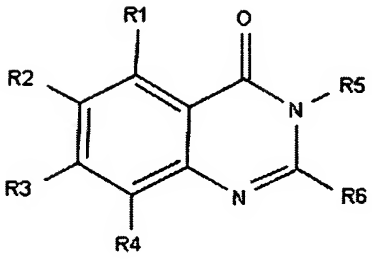
Claims

1. A compound of the formula (I), or pharmaceutically acceptable salts or solvates thereof,

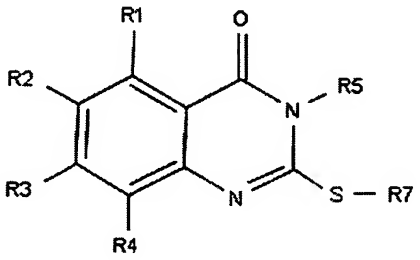


(I)

wherein the substitutents and indices have the following meanings:

R_1, R_2, R_3 and R_4, is H, halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or substituted or unsubstituted phenyl,
R_5 is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl
R_6 is H, a secondary or a tertiary amine, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl

2. A compound according to claim 1, or pharmaceutically acceptable salts or solvates thereof, of formula (II)

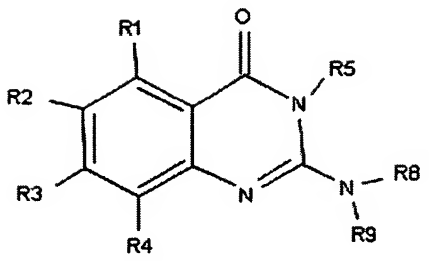


(II)

wherein the substitutents and indices have the following meanings:

R_7 is C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl

3. A compound according to claim 1, or pharmaceutically acceptable salts or solvates thereof, of formula (III)



(III)

Wherein the substituents and indices have the following meanings:

R_1, R_2, R_3, R_4, is H, halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl,

R_5 in formula (III) is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl,

R_8 in formula (III) is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl)amino or phenyl,

R_9 in formula (III) is H, C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N- (phenylsulfonyl)amino or phenyl,

R_8 and R_9 in formula (III) are taken together with the N in formula (III) to form a ring of the following types:

C_3 to C_8 mono, di- or tri- heteroatom-substituted cycloalkyl, preferably piperidino, morpholino, thiomorpholino, piperazino, or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof,
C_4 to C_{10} mono, di- or tri- heteroatom-substituted bi- or tricycloalkyl derivatives thereof or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof,
C_3 to C_8 mono, di- or tri- heteroatom-substituted heteroaryl, preferably pyrrolo, pyrazolo, oxazolo, thiazolo, pyridino, pyridazino, pyrimidino, pyrazino, triazino, indolo, quinolino, quinazolino, or C_1 to C_6 alkyl-, C_1 to C_6 substituted alkyl subtituted- or benzocondensated derivatives thereof

4. A compound according to claim 3 wherein

R_1 and R_3 are H,
R_2 and R_4 are H, or iodo, bromo, chloro or fluoro or hydroxy methyl, trifluoromethyl, methoxy, amino, alkylated amino, or nitro
R_5 is H, C_1 to C_8 alkyl, preferrably isopropyl, vinyl, 2-isobutyl, or cyclohexyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl,
R_8 and R_9 in formula (III) are taken together with the N in formula (III) to form a ring of the following types:

C_3 to C_8 mono, di- or tri- heteroatom-substituted cycloalkyl, preferably piperidino, morpholino, thiomorpholino, piperazino, or C_1 to C_6 alkyl-C_1-C_6 substituted or benzocondensated derivatives thereof, more preferrably a 4-aryl- or 4-heteroaryl- or 4-alkyl-substituted piperazino or a 4-alkyl-substituted piperidino

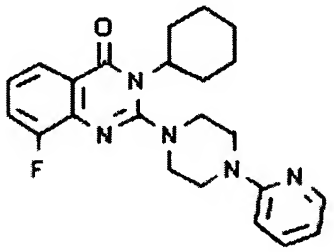
C_4 to C_{10} mono, di- or tri- heteroatom-substituted bi- or tricycloalkyl or C_1 to C_6 alkyl-, C_1-C_6 substituted alkyl substituted- or benzocondensated derivatives thereof

C_3 to C_8 mono, di- or tri- heteroatom-substituted heteroaryl, preferably pyrrolo, pyrazolo, oxazolo, thiazolo, pyridino, pyridazino, pyrimidino, pyrazino, triazino, indolo, quinolino, quinazolino or C_1 to C_6 alkyl- C_1 to C_6 substituted alkyl substituted- or benzocondensated derivatives thereof

5. A compound according to any of claims 1 to 3 wherein

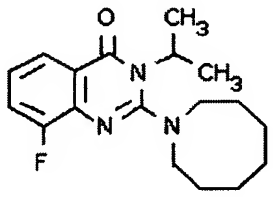
R_1 and R_3 are H,
R_2 and R_4 are H, or iodo, bromo, chloro or fluoro or hydroxy methyl, trifluoromethyl, methoxy, amino, alkylated amino, or nitro
R_5 is H, C_1 to C_8 alkyl, preferrably isopropyl, vinyl, 2-isobutyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, aryl, substituted aryl, C1 to C6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl,
R_8 is a C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, preferrably benzyl or (furan-2-yl)-methyl or (thiophen-2-yl)-methyl
and R_9 in formula is C_1 to C_8 alkyl, C_1 to C_8 substituted alkyl, C_3 to C_8 cycloalkyl, C_3 to C_8 substituted cycloalkyl, C_1 to C_6 alkylphenyl or C_7 to C_{12} substituted phenylalkyl, preferably (ethyl)-propion-1-yl

6. A compound according to any of claims 1 to 5 being



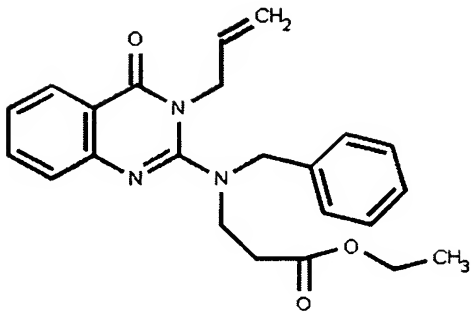
(IV)

7. A compound according to any of claims 1 to 5 being



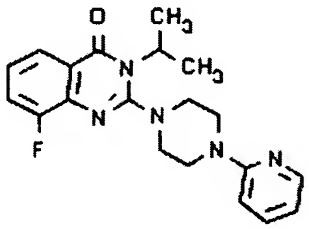
(V)

8. A compound according to any of claims 1 to 5 being



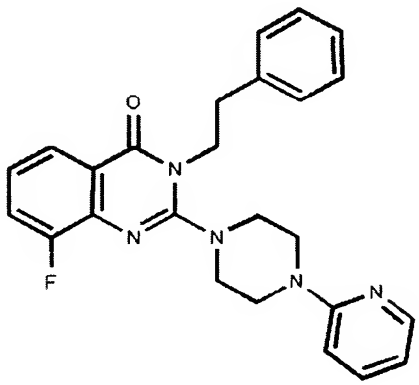
(VI)

9. A compound according to any of claims 1 and 5 being



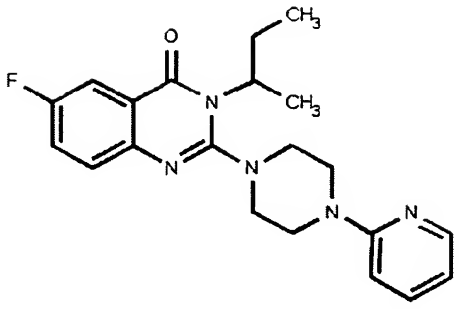
(VII)

10. A compound according to any of claims 1 and 5 being



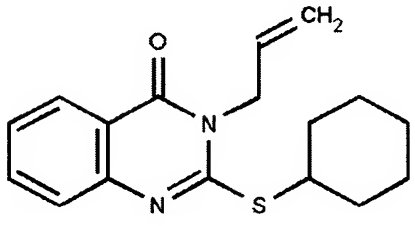
(VIII)

11. A compound according to any of claims 1 and 5 being



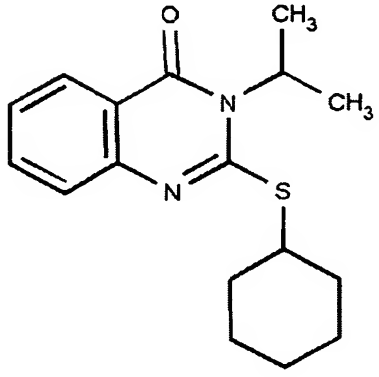
(IX)

12. A compound according to any of claims 1 and 5 being



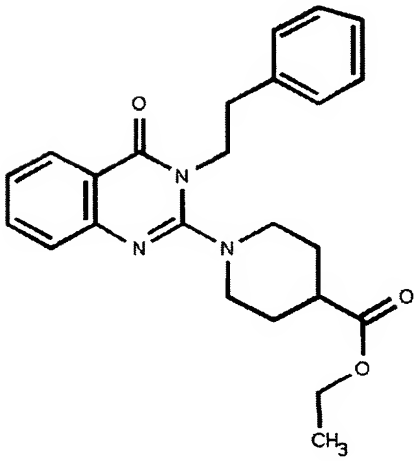
(X)

13. A compound according to any of claims 1 and 5 being



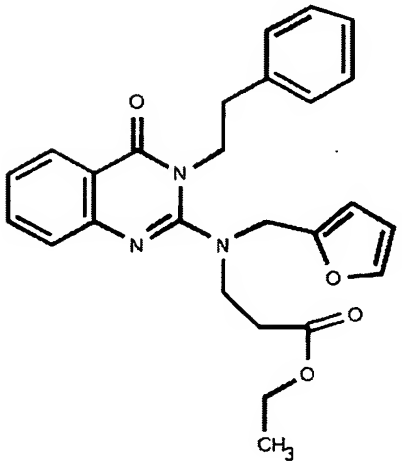
(XI)

14. A compound according to any of claims 1 and 5 being



(XII)

15. A compound according to any of claims 1 and 5 being



(XIII)

16. A compound according to any of claims 1 to 15 wherein said compound is capable of binding the NR1H3 receptor protein encoded by a nucleic acid comprising SEQ ID NO:2 or a portion thereof or a mammalian homologue thereof.

17. A compound according to any of claims 1 to 15 wherein said compound is capable of binding the NR1H2 receptor protein encoded by a nucleic acid comprising SEQ ID NO:1 or a portion thereof or a mammalian homologue thereof.

18. A compound according to any of claims 1 to 15 for use as a medicament.

19. A method for prevention or treatment of a NR1H3 and/or NR1H2 receptor protein mediated disease or NR1H3 and/or NR1H2 receptor protein homologue mediated disease or condition in a mammal comprising administration of a therapeutically effective amount of a compound according to claims 1 to 15 wherein the prevention or treatment is directly or indirectly accomplished through the binding of the compound according claims 1 to 15 to the NR1H3 and/or NR1H2 receptor proteins or to the NR1H3 and/or NR1H2 receptor protein homologues.

20. A method for regulating the cholesterol synthesis or transport in a mammal which comprises activating the NR1H3 and/or NR1H2 receptors with a therapeutically effective amount of a compound according to claims 1 to 15.

21. A method of treating in mammal a disease which is affected by cholesterol, triglyceride, bile acid, glucose or glucocorticoid levels comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to claims 1 to 15.

22. A method of treating in a mammal Atherosclerosis, Alzheimers disease, Type II diabetes, lipid disorders, obesity, an inflammatory or a cardiovascular disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound according to claims 1 to 15.

23. A method according to any of claims 19 to 22, wherein the expression of one or more of the genes out of the group comprising ABCA1, ABCG1, ABCG5, ABCG8, apolipoprotein-CI, -CII, -CIV, -E, LPL (lipoprotein lipase), CETP (cholesteryl ester transfer protein) or other genes that positively regulate cholesterol homeostasis is increased upon compound administration.

24. A method according to any of claims 19 to 22, wherein the expression of one or more of the genes out of the group comprising 11-β-HSD (11-β hydroxysteroid dehydrogenase), PEPCK (phosphoenolpyruvat carboxykinase), G-6-P (glucose-6-phosphatase) is reduced upon compound administration.

25. A method according to any of claims 19 to 22, wherein the expression of one or more of the genes out of the group comprising FAS (Fatty Acid Synthase), SREBP-1c (Sterol-response element binding protein), SCD-1 (Stearoyl-CoA Desaturase), Angiopoietin like protein 3 (Angptl3) or other genes which are relevant for controlling serum triglyceride or glucose levels are not or more weakly increased in liver and or other organs compared to administration of a full agonist like T0901317.

26. A method of blocking in a mammal the cholesterol or fatty acid absorption in the intestine of a mammal in need of such blocking comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined in any of claims 1 to 15.

27. A method for treating obesity in a mammal comprising administring a therapeutically effective amount of a compound as defined in any of claims 1 to 15.

28. A method of modulating a gene whose expression is regulated by the NR1H3 and/or NR1H2 receptor in a mammal comprising administering a therapeutically effective amount of a compound as defined in any claims 1 to 15.

29. A method according to any of claims 19 to 28 wherein the expression of ABCA1 and/or ABCG1 and/or ABCG5 and/or ABCG8 is increased.

30. Use of a compound as defined in any of claims 1 to 15 in a method according to claims 19 to 29 wherein the mammal is a human.

31. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for the prevention or treatment of a NR1H3 and/or NR1H2 receptor protein or NR1H3 and/or NR1H2 receptor protein homologue mediated disease or condition in a mammal wherein the prevention or treatment is directly or indirectly accomplished through the binding of the compound to the NR1H3 and/or NR1H2 receptor protein or NR1H3 and/or NR1H2 receptor protein homologue.

32. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for prevention or treatment of a NR1H3 and/or NR1H2 receptor protein mediated disease or condition wherein the mammal is a human.

33. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for regulating the cholesterol transport system in a mammal by activating the NR1H3 and/or NR1H2 receptor.

34. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for regulating levels of cholesterol, triglyceride, and/or bile acid.

35. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for treating in a mammal atherosclerosis, Alzheimer disease, gallstone disease, lipid disorders, inflammatory disorder, type II diabetis, obesity or a cardiovascular disorder.

36. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament capable for blocking in a mammal the cholesterol and/or fatty acid absorption in the intestine.

37. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for treating obesity in a mammal.

38. Use of a compound as defined in any of claims 1 to 15 for the manufacture of a medicament for modulating a gene whose expression is regulated by the NR1H3 and/or NR1H2 receptor.

39. Use of a compound as defined in any of claims 1 to 15 in a mammal for the selective up-regulation of one or more genes selected from the group comprising ABCA1, ABCG1, ABCG5, ABCG8, apolipoprotein-CI, -CII, -CIV, -E, LPL (lipoprotein lipase), CETP (cholesteryl ester transfer protein) or other genes that positively regulate cholesterol homeostasis are increased and a weaker regulation of one or more of the genes selected from the group comprising FAS and SREBP-1c or other genes that positively regulate lipogenesis, said compound showing a larger difference in regulation of the two groups of genes when compared with the regulatory behaviour of a full agonist like T0901317 on both groups of genes.

40. The use according to any of claims 31 to 39, wherein the mammal is human.

Fig.1

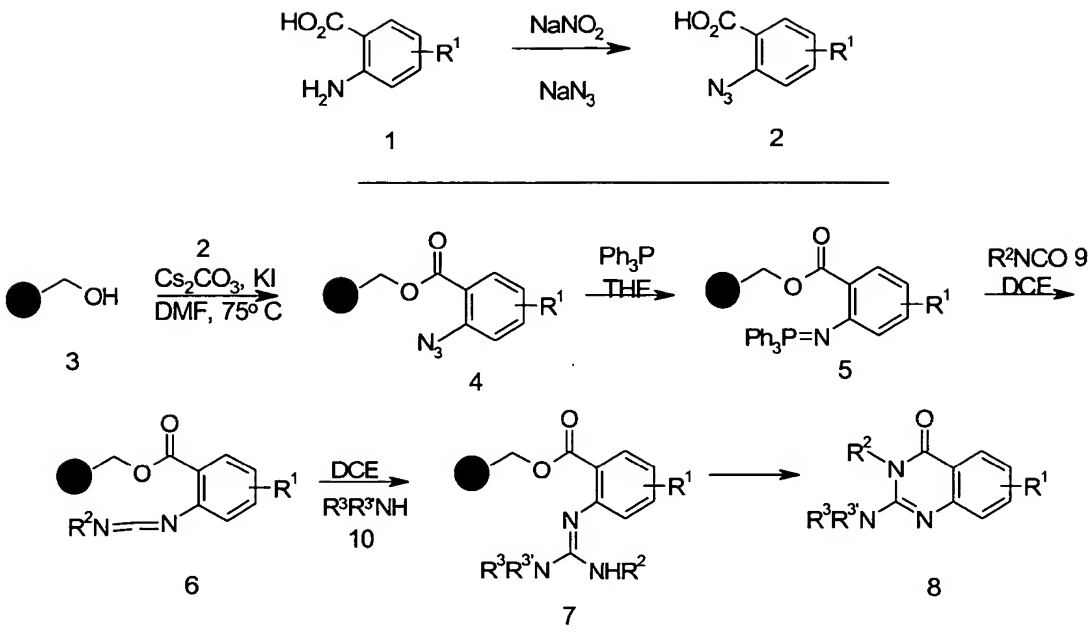

HO2C
R1
H2N
NaNO2
NaN3
N3
1
2
OH
2
Cs2CO3, KI
DMF, 75° C
3
4
Ph3P
THF
Ph3P=N
5
R2NCO 9
DCE
R2N=N
6
DCE
R3R3'NH
10
R3R3'N
NHR2
7
R2
8

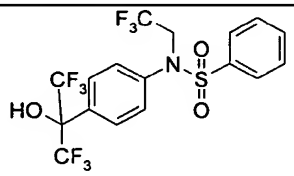
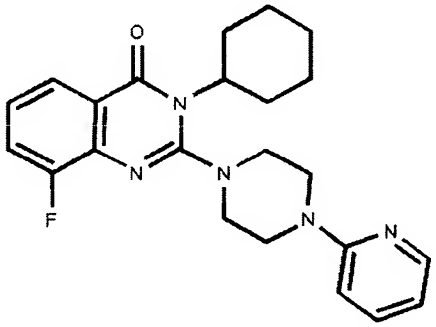
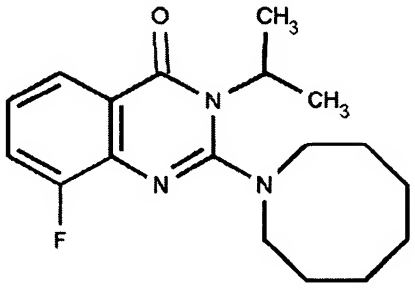
Fig. 2

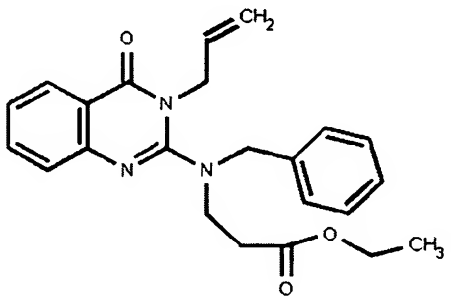
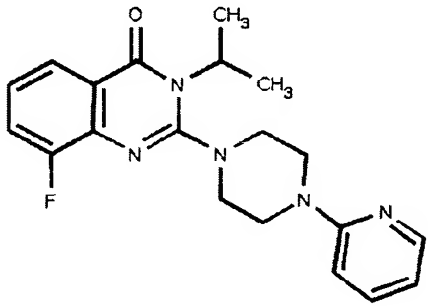
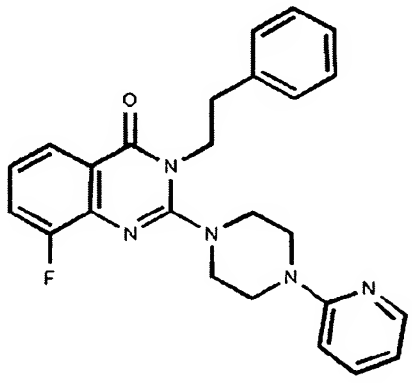
Number of repeats 1
plate: GREINER FIA-Plate black 384 well med. binding
Measurement height ..... 3.50 mm
Label technology ..... TR-F Lance
Emission filter name D615
Emission filter slot A1
Emission aperture ..... Normal
Excitation filter D340
Delay ..... 50 µs
Window time ..... 400 µs
Cycle ..... 1000 µs
Light integrator capacitors 1
Light integrator ref. level 95
Flash energy area ..... High
Flash energy level 223
Flash absorbance measurement ..... No
Beam ..... Normal
Label technology ..... TR-F Lance
Emission filter name D665
Emission filter slot A8
Emission aperture ..... Normal
Excitation filter D340
Delay ..... 50 µs
Window time ..... 400 µs
Cycle ..... 1000 µs
Light integrator capacitors 1
Light integrator ref. level 95
Flash energy area ..... High
Flash energy level 223
Flash absorbance measurement ..... No
Beam ..... Normal

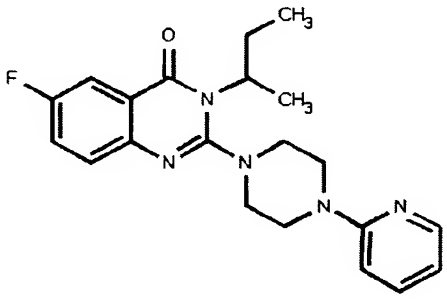
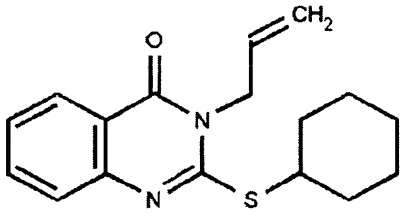
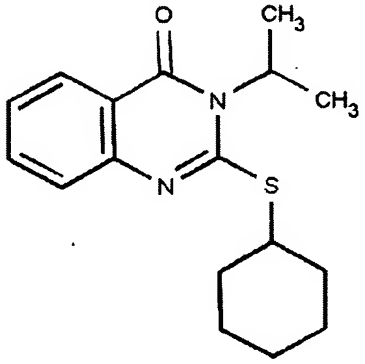
Fig. 3

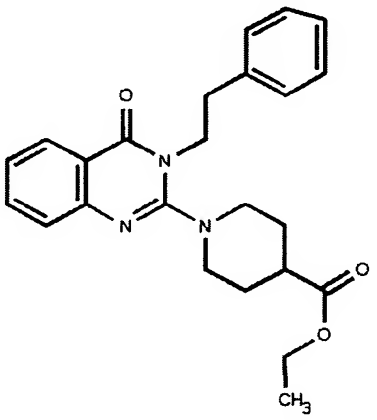
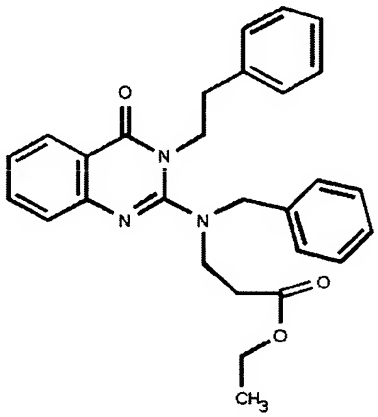
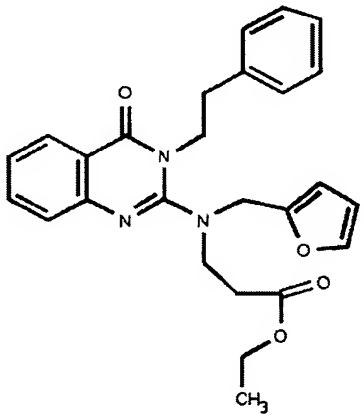
Gene definition	NCBI Accession number of gene	Corresponding SEQ ID Number
Liver X receptor beta NR1H2	NM_007121	1
Liver X receptor alpha NR1H3	NM_005693	2
Steroid receptor coactivator 1	U90661	3

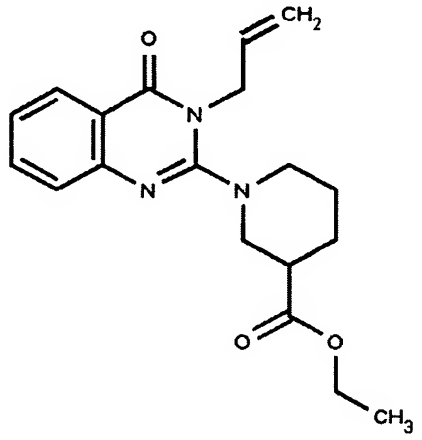
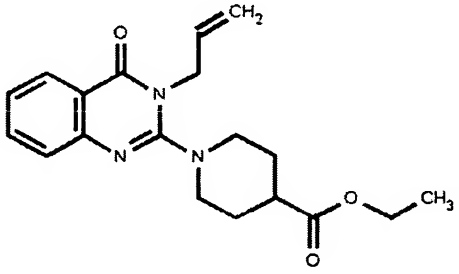
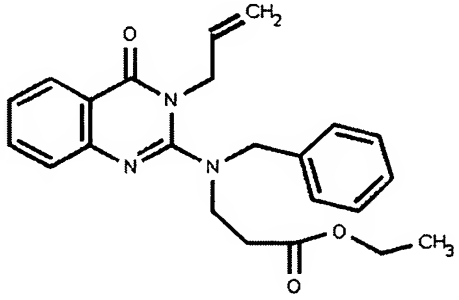
Fig. 4

MOLNAME	MOLECULE STRUCTURE	EC50 AVG [μM]	% EFIC AVG
TO901317	 TO901317	0,1	100
LN0000007033		5	50
LN0000007025		4	60

LN0000007184		0,5	130
LN0000007031		4	50
LN0000007032		42	150

LN0000006672			
LN0000007172		1,1	21
LN0000007174		32	>100

LN0000007179		0,8	127
LN0000007180		0,16	128
LN0000007181		0,12	89

LN0000007182		2,4	108
LN0000007183		2,6	117
LN0000007184		0,55	130

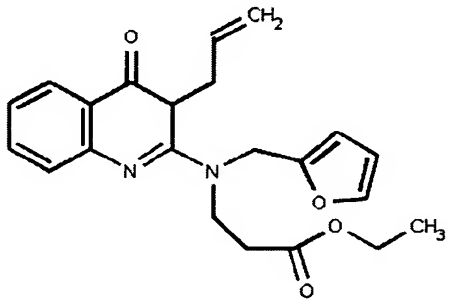
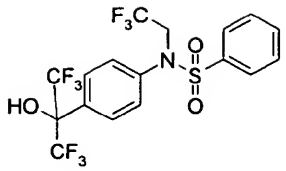
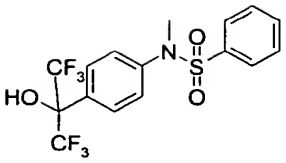
LN0000007185		0,34	142

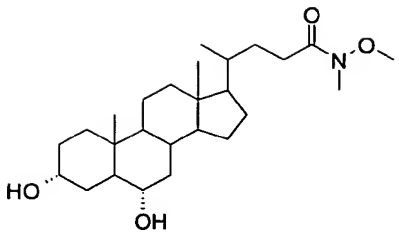
Fig. 5



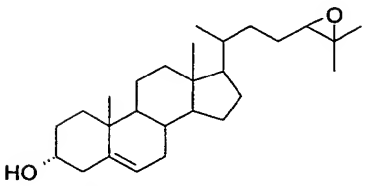
TO901317



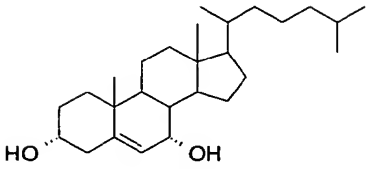
TO314407



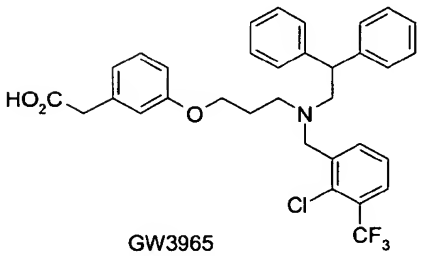
Hypocholamide



24(S),25-Epoxycholesterol



7a-Hydroxycholesterol



GW3965

Fig. 6

Protein / Gene Name	NCBI Acccesion number of gene	Corresponding SEQ ID number
Liver X receptor beta, LXRß	NM_007121	1
Liver X receptor alpha, LXRα	NM_005693	2
Cholesterol 7 α hydroxylase, Cyp7A1	NM_000780	3
Fatty Acid Synthase FAS	NM_004104	4
Stearyl CoA desaturase, SCD	XM_030447	5
Sterol Response Element Binding Protein 1C, SREBP-1C	NM_004176	6
ATP binding cassette transporter A1; ABCA1	NM_005502	7
ATP binding cassette transporter G1; ABCG1	XM_032950	8
ATP binding cassette transporter G5; ABCG5	NM_022436	9
ATP binding cassette transporter G8; ABCG8	AF324494	10
Apolipoprotein E, apoE	NM_000041	11
Apolipoprotein C-I, apoC-I	NM_001645	12
Apolipoprotein C-II apoC-II	NM_000483	13
Apolipoprotein C-IV, apoC-IV	U32576	14
Lipoprotein Lipase, LPL	M15856	15
Cholesteryl Ester Transfer Protein, CETP	NM_000078	16
Phosphoenolpyruvate carboxykinase 1 (PEPCK)	NM_002591	17
Glucose-6-phosphatase (G6P)	NM_000151	18
Insulin-responsive glucose transporter (GLUT4)	M20747	19
Angiopoietin-like 3, ANGPTL3	NM_01445	20
11-beta Hydroxysteroid dehydrogenase HSD11B1 variant 2	NM_181755	21
11-beta Hydroxysteroid dehydrogenase HSD11B1 variant 1	NM_005525	22

Fig. 7

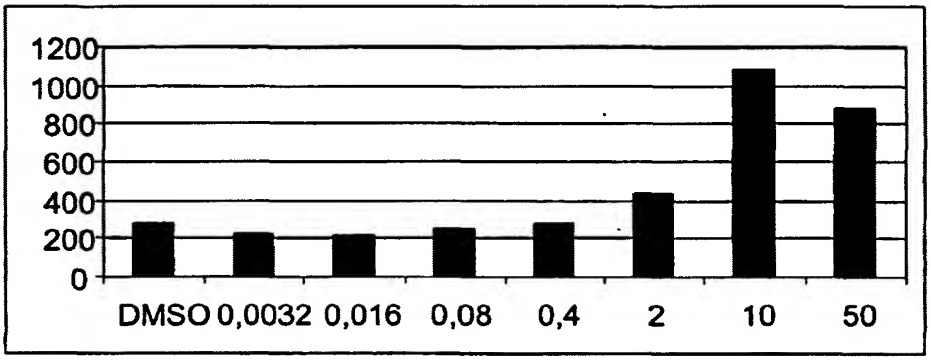


Fig. 8A

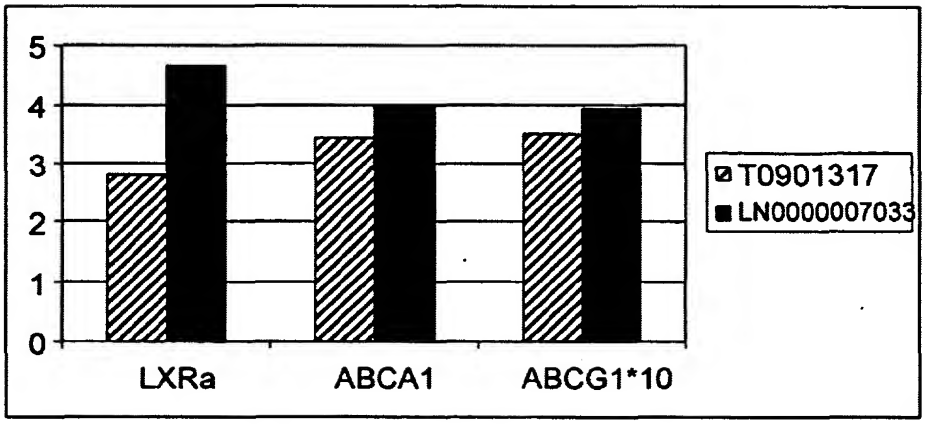

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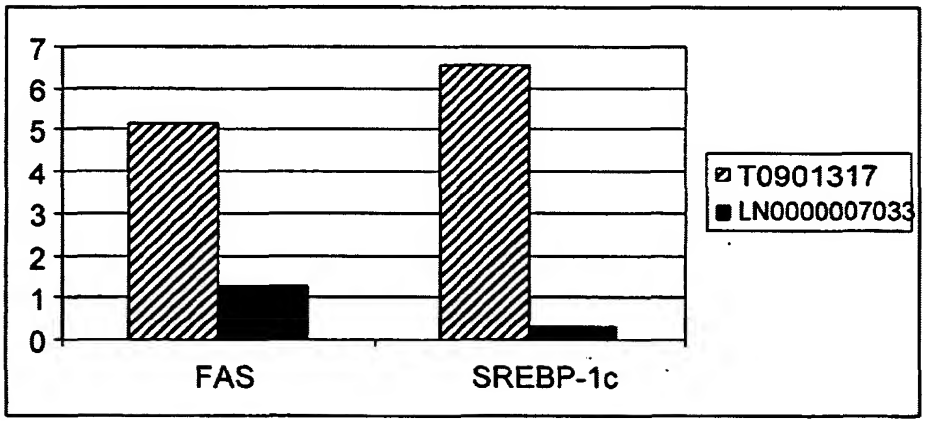
Fig. 8B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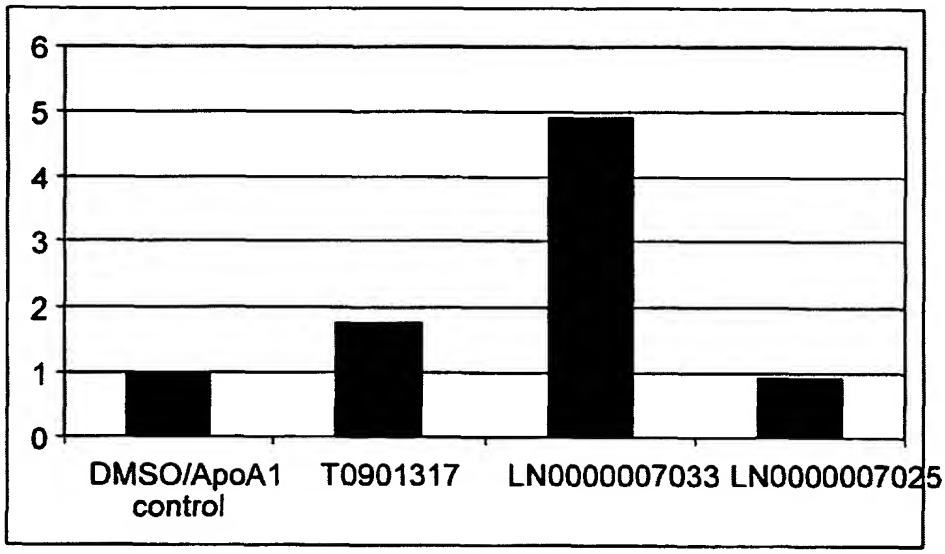
LN0000007033

Fig. 9 A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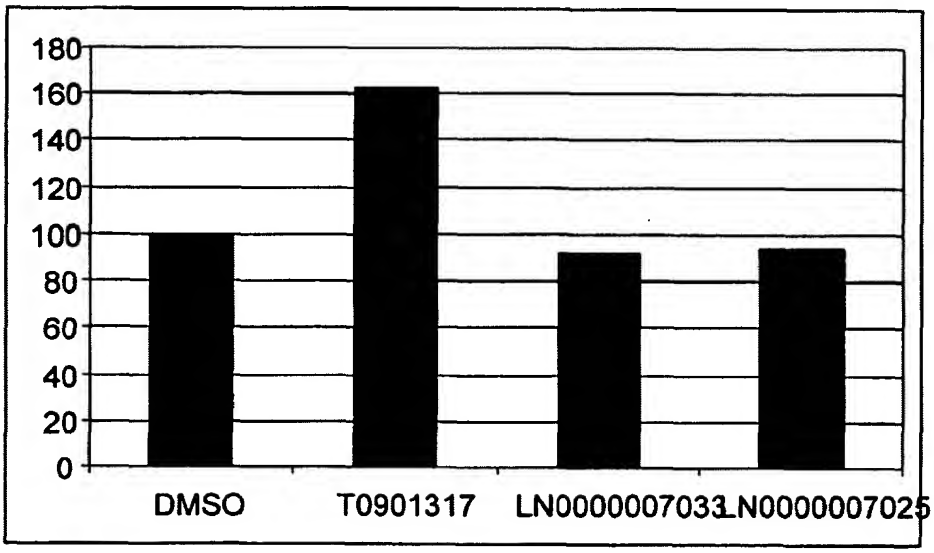
DMSO/ApoA1 control
T0901317
LN0000007033
LN0000007025

Fig. 9 B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DMSO
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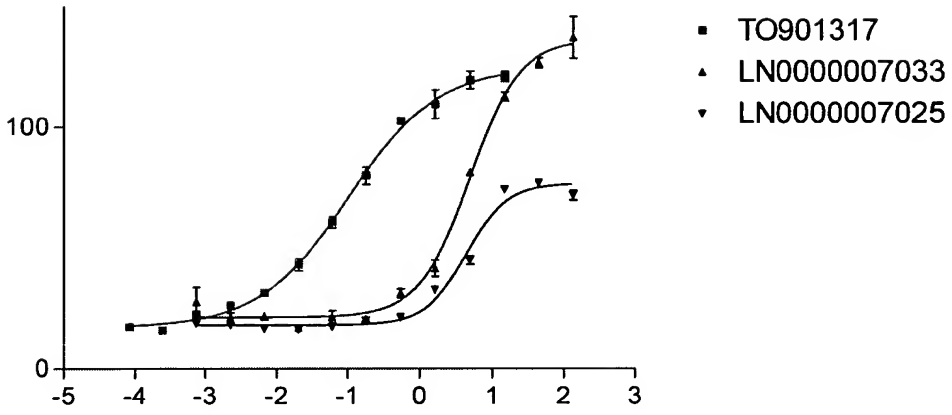
LN0000007033
LN0000007025

Fig. 10



European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 03 02 0417

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 02/062798 A (REDDY RESEARCH FOUNDATION) 15 August 2002 (2002-08-15) * claim 1 * * page 106, line 22 - page 107, line 6 * * page 1, line 17 - page 2, line 16 * -----	1,3-5, 16-40	A61K31/517 C07D239/95 C07D401/12 C07D405/12 A61P3/06
X	WO 97/20823 A (CRISCIONE LEOLUCA ;YAMAGUCHI YASUCHIKA (CH); CIBA GEIGY AG (CH); M) 12 June 1997 (1997-06-12) * page 74; example 28 * * page 1, paragraph 1 * * claim 12 * -----	1,3,5, 16-40	
X	WO 02/48152 A (BAKTHAVATCHALAM RAJAGOPAL ;BRIELMANN HARRY L (US); ELLIOTT RICHARD) 20 June 2002 (2002-06-20) * page 59; example 12 * * page 6, paragraph 17 * -----	1,3,4, 16-40	
X	US 3 609 152 A (HESS HANS-JURGEN E ET AL) 28 September 1971 (1971-09-28) * examples III-X * -----	1,3-5, 16-40	
	-/--		TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07D A61K A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
Munich	10 December 2003	Kollmannsberger, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

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INCOMPLETE SEARCH SHEET C

Application Number
EP 03 02 0417

Claim(s) searched completely:
6-15

Claim(s) searched incompletely:
1-5, 16-40

Reason for the limitation of the search:

Claims 1-5 encompass a large number of known compounds. Also the use of these compounds in the treatment of diseases as listed e. g. in claim 22 appears to be well known. The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search is only complete for:

Compounds according to claim 1 which are explicitly stated in the prior art to have binding affinity to the LXR receptor; compounds as such according to claims 5-16.

Only some documents relevant to other subject-matter of the claims have been cited for illustration.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 03 02 0417

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 01/021598 A (ASTRAZENECA UK LTD ; ASTRAZENECA AB (SE)) 29 March 2001 (2001-03-29) * claims 1,10 *	1,3, 16-40	
X	US 6 337 332 B1 (CARPINO PHILIP A) 8 January 2002 (2002-01-08) * column 1 * * examples 1-7 * * tables 1-5 *	1,16-40	
X	HESS, HANS J. ET AL: "Antihypertensive 2-amino-4(3H)-quinazolinones" JOURNAL OF MEDICINAL CHEMISTRY , 11(1), 130-6 CODEN: JMCMAR; ISSN: 0022-2623, 1968, XP002264555 * column 1, paragraph 1 * * page 132 - page 133; table 1 *	1,3-5, 16-40	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	GUPTA C M ET AL: "Drugs acting on the central nervous system. Syntheses of substituted quinazolones and quinazolines and triazepino- and triazocinoquinazolones" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 11, no. 2, 26 February 1968 (1968-02-26), pages 392-395, XP002156695 ISSN: 0022-2623 * examples 4-7,13-16,20,22,23,38; table 2 *	1-5,18	
	-/--		

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 03 02 0417

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ZAIDI, NAFEESA B. ET AL: "Synthesis of some new 4(3H)-quinazolones and their derivatives as possible antitubercular agents" XP002264556 retrieved from STN Database accession no. 1982:616118 * abstract * & ACTA CIENCIA INDICA, CHEMISTRY , 7(1-4), 63-8 CODEN: ACICDV; ISSN: 0253-7338, 1981, -----	2,18	
X	MANABU HORI ET AL: "Novel 4-Substituted 2-Piperazinylquinazolines as potent Anticonvulsive and Antihypoxic Agents" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 38, no. 5, 1990, pages 1286-1291, XP002128282 ISSN: 0009-2363 * examples 3A-3H; table II * -----	1,3-5	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002225148 Order Number: TRG10400#07364-D; TRG10400#01891-D; TRG10400#01815-D; TRG10400#01814-D; TRG10400#01812-D; TRG10400#01811-D; TRG10400#01809-D; TRG10400#01736-D; TRG10400#01735-D; TRG10400#01732-D; TRG10400#01729-D -/--	1,3-5	

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 03 02 0417

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	& "Chem.Folio" 15 January 2001 (2001-01-15), LION BIOSCIENCE AG , HEIDELBERG, GERMANY -----		
X	US 3 867 384 A (SHEERAN PATRICK J ET AL) 18 February 1975 (1975-02-18) * column 1 - page 2 * * column 5; table 1 * -----	1-5	
X	US 3 755 582 A (BULLOCK G) 28 August 1973 (1973-08-28) * examples 1-6,8,12-14 * -----	2	
A	WO 02/24632 A (GLAXO GROUP LTD ; COLLINS JON LOREN (US); FIVUSH ADAM M (US); MALONEY) 28 March 2002 (2002-03-28) * claims * -----	1-40	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 03 02 0417

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10-12-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02062798 A	15-08-2002	CA 2436738 A1	15-08-2002
		EP 1363913 A2	26-11-2003
		WO 02062798 A2	15-08-2002
		CA 2436741 A1	15-08-2002
		EP 1363914 A1	26-11-2003
		WO 02062799 A1	15-08-2002
		US 2002169175 A1	14-11-2002
WO 9720823 A	12-06-1997	AU 7692996 A	27-06-1997
		WO 9720823 A2	12-06-1997
		ZA 9610020 A	01-06-1997
WO 0248152 A	20-06-2002	AU 2027602 A	24-06-2002
		EP 1347982 A2	01-10-2003
		WO 0248152 A2	20-06-2002
		US 2003036652 A1	20-02-2003
US 3609152 A	28-09-1971	BE 678216 A	22-09-1966
		DE 1620127 A1	12-03-1970
		FR 5267 M	31-07-1967
		GB 1062357 A	22-03-1967
		GB 1174272 A	17-12-1969
		GB 1174273 A	17-12-1969
WO 0121598 A	29-03-2001	AU 7031500 A	24-04-2001
		EP 1218358 A1	03-07-2002
		WO 0121598 A1	29-03-2001
		JP 2003509501 T	11-03-2003
		US 6399603 B1	04-06-2002
US 6337332 B1	08-01-2002	NONE	
US 3867384 A	18-02-1975	NONE	
US 3755582 A	28-08-1973	NONE	
WO 0224632 A	28-03-2002	AU 1121602 A	02-04-2002
		EP 1318976 A2	18-06-2003
		WO 0224632 A2	28-03-2002

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82